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PHYSIOLOGICAL CONDITIONS

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COMPARISON OF CHANGES IN CARDIAC AND RESPIRATORY RHYTHMS EFFECTED IN THE DOG BY CHANGES IN PHYSIOLOGICAL CONDITIONS^{1,2}

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The experiments described in this paper were designed to study the early effects of low alveolar oxygen, of high alveolar carbon dioxide, of mechanical asphyxia, and of intravenous injections of sodium cyanide, sodium sulphide, sodium bicarbonate and sodium carbonate on the respiratory and cardiac rhythms of the anesthetized dog. Tentatively, it was assumed that a similarity of response in these physiological rhythms might be indicative of a common mechanism operating at the pace-setter of respiratory movements, and at the pace-setter of cardiac contractions in the same animal (Gesell and Nyboer, 1929b)

METHOD. Nearly a hundred dogs weighing from 7 to 32 kgm. were used. They were anesthetized by injection of about 7 mgm. of morphine sulphate and about 1.0 gram of urethane per kilogram body weight. The trachea was connected to an improved triple unit rebreathing tank (Gesell, 1930) from which the expired carbon dioxide was absorbed by soda-lime (except in carbon dioxide rebreathing experiments). Three to ten per cent oxygen mixtures and five to thirty-eight per cent carbon dioxide mixtures with 22 per cent or more of oxygen were rebreathed at ordinary atmospheric pressures for periods of from one to four minutes. The following solutions were injected in variable amounts into the femoral vein: M/100 sodium cyanide and M/8 sodium sulphide dissolved in physiological saline solution, M/1 sodium bicarbonate (prepared just prior to injection) and M/2 sodium carbonate dissolved in distilled water. Mechanical asphyxiation was produced at the end of inspiration and at the end of expiration by obstructing the tracheal cannula. The blood pressure was recorded with a mercury manometer from the femoral artery.

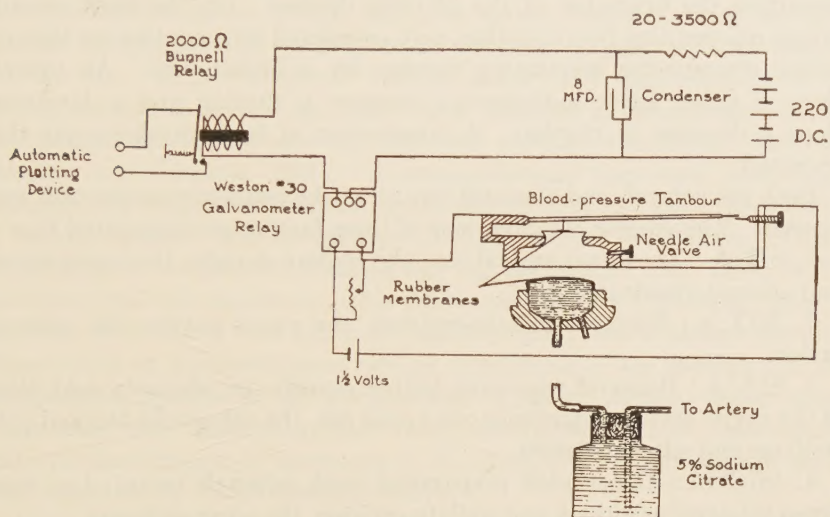
In the earlier experiments the cardiac and respiratory rhythms were counted, the former from the blood pressure tracing, and plotted as ordi-

¹ Preliminary reports. Proc. Soc. Exper. Biol. and Med., 1929, xxvi, 832. Proc., This Journal, 1932, ci, 80.

² Submitted in partial fulfillment of the requirements for the degree of Doctor of Science.

nates against time as abscissae on the kymograph tracings, but in more recent experiments the two sets of rhythmic changes were plotted automatically and simultaneously by a special device of Gesell (1930).³ The closing of an electrical key mounted on a mean blood pressure tambour

PULSE BEAT CONTACT DEVICE AND CIRCUIT



RESPIRATORY MOVEMENT CONTACT DEVICE AND CIRCUITS

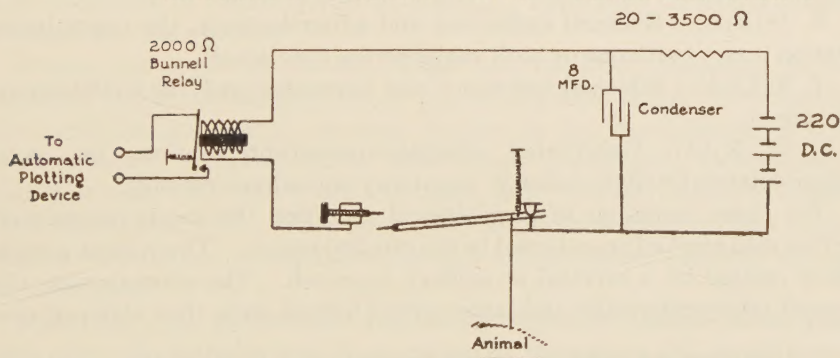


Fig. 1

activated the cardiac rhythm plotter through a system of relays during each diastole of the heart, and the closing of an electrical pneumograph key activated the respiratory rhythm plotter during each inspiratory

³ Demonstrated at the meetings of the American Physiological Society March, 1930.

movement. The diagrams of the electrical circuits involved are self explanatory (see fig. 1). Electrolytic condensers were employed to provide momentary activation of the plotting devices and to avoid the objectionable fusion of contacts. A further advantage of this method was obtained in that positive contacts were assured, as the electrical keys could be closed during any fraction of diastolic or inspiratory time without impairing the operation of the plotting devices. On the fixed records, points representing heart rhythm were connected by a continuous line and points representing respiratory rhythm by a broken line. An upward slope of either curve indicates an increase in rhythm and a downward slope a decrease in rhythm. A comparison of both rhythms was thus obtained.

Both the nervous and humoral control of the heart and respiration were altered. The various combinations of these factors are designated thus:⁴

1. S.X.A.: The intact animal; i.e., the stellate ganglia, the vagus nerves and adrenals intact.

2. (S)X.A.: Bilateral stellate-excision, the vagus nerves and adrenals intact.

3. S(X)A.: Bilateral vagotomy (either excision or adequate cold block of the vagus nerves; sometimes one vagus cut, the other cold blocked), the stellates and adrenals intact.

4. (S)(X)A.: Denervated preparation with adrenals intact; i.e., combined bilateral vagotomy and stellate-excision, the adrenals intact.

5. S.X.(A).: Bilateral adrenalectomy,⁵ the vagus and stellate innervations intact.

6. (S)X(A).: Bilateral stellotomy and adrenalectomy, the vagus innervation intact (with one or both vagus nerves functional).

7. S(X)(A).: Bilateral vagotomy and adrenalectomy, the stellate ganglia intact.

8. (S)(X)(A).: Denervated adrenalectomized-preparation; i.e., combined bilateral stellate-excision, vagotomy and adrenalectomy.

For these variations of physiological condition the vagus nerves were either cold blocked or sectioned in the cervical region. The stellate ganglia were excised by a cervical or axillary approach. The adrenals were dissected retroperitoneally and large curved forceps were then clamped over

⁴ In the paper and tables parentheses are used and in the illustrations circles are circumscribed around the letters S, X and A.

⁵ In contrast to Vincent and Thompson's observations (1930) on cats, adrenalectomy in the dog with innervations intact usually resulted in tachycardia and a rise in blood pressure. Subsequently there was a gradual lowering of the blood pressure. Abnormally low blood pressure and a lower heart rate developed following additional excision of the stellate ganglia. A marked fall in blood pressure was likewise noted if adrenalectomy followed stellate ganglia removal. Similar lowerings of blood pressure and heart rate were obtained with and without vagotomy.

each adrenal gland to occlude the venous and arterial supply and to crush the innervation. The clamping of the structures of the hilum was confirmed by autopsy observations.

In an (S)(X)(A) preparation the heart is freed of its adrenal gland control and of its major extrinsic accelerating and inhibiting nervous control. In this connection attention should be called to the experiments of Cannon and his co-workers (1926), who have shown that stellotomy does not remove all sympathetic connections to the heart in recovery experiments on the cat. With "complete" cardiac denervation and removal of all known cardio-accelerator agencies a slow increase in cardiac rate, which was attributed to "sympathin," followed psychic stimulation (Newton, Zwemer and Cannon, 1931). In unanesthetized dogs with denervated adrenals and "complete" cardiac denervation McIntyre (1931) did not find a change in heart rate in response to slight animal movements. Other experimental evidence of Cannon and his associates (1921, 1924, 1927), indicates that full anesthesia (with ether, urethane, or chloralose) greatly reduces (to within 1 or 2 beats per minute) and often abolishes the phenomenon of an increased heart rate on stimulation of the muscles and the sympathetic system in cat preparations in which adrenal denervation, vagotomy and stellate-excision were performed. Thus experiments indicate that changes in heart-rate in the (S)(X)(A) preparation are probably the result of direct chemical action.

Denervation of the pace-setter of respiratory movements is incomplete in the present experiments. As is well known, vagotomy removes important influences of respiratory reflex-control. The effects of stellate ganglia excision are less obvious.

Among the important factors, which may influence respiration in the so-called denervated-preparation, is the carotid-sinus reflex. The respiratory response to various chemical changes in the blood-stream is very much affected by carotid-sinus denervation (Bouckaert, Dautrebande, and Heymans, 1931; and Gesell and Owen, 1931; Winder, Owen and Gesell, 1932; Bernthal, 1932). This reflex offers an additive effect to that of the central stimulation of respiration brought about during chemical change in the animal.

RESULTS. The cardiac and respiratory rhythmic changes developing soon after the introduction of experimental procedures fall roughly into four general types diagrammatically represented in figure 2. Type I shows a primary acceleration of both cardiac and respiratory rhythms and slowing with recovery; type II shows a primary slowing of both rhythms; type III curve shows a slowing of heart rhythm and acceleration of respiratory rhythm; type IV curve shows an acceleration of cardiac rhythm and a decreased respiratory rhythm. Sometimes a change in rhythm failed to appear. Sometimes, during the return toward the normal rate, one or

both rhythms continued to decrease or increase to a rate below or above the basal level, before returning permanently to the basal rate.

The general data obtained with respect to cardiac and respiratory rhythms under each experimental condition are summarized in table 1. Vagotomy and stellate-excision are indicated by the column headings (S).(X)., S.(X)., (S).X., S.X., while the condition of the adrenals is indicated by the A or (A) in the extreme left column headed experimental procedure. The type of reaction, the percentage and number of similar reacting dogs are listed. Table 2 supplements table 1 and gives the average cardiac and respiratory rhythms. Part I of this table lists the average basal rates of each rhythm before experimental procedures in each type of preparation. Part II gives the average percentage change in

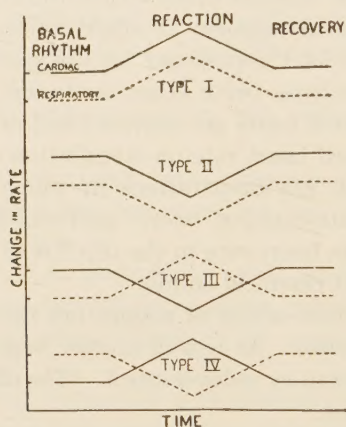


Fig. 2. Diagram representing the four types of changes in cardiac and respiratory rhythms obtained in these studies. Upstroke of either curve indicates acceleration and downstroke indicates slowing of the rhythm. Throughout the paper, similar changes are referred to as types I, II, III, and IV.

primary cardiac and respiratory rhythm, i.e., response above or below the basal rates. Only predominant reactions are averaged in these data. Comparison of these averages is a qualitative one as the injection of solutions and the administration of gases were not standardized. Typical semi-schematic drawings of predominant cardiac and respiratory reactions to given experiments are presented in figures 3, 4, and 5.

In general when the (S)(X)(A) preparations were subjected to experiment, a constant type of response was obtained. In contrast to this, the intact animal with complete innervation and functional adrenals (S.X.A) showed a decidedly variable response. (See table 1.)

Specific results are presented in the order shown in table 1.

A. *The effect of low oxygen on the cardiac and respiratory rate.* (See fig. 3, and tables 1 and 2.) Various workers have reported the effects of

low alveolar oxygen on the cardiac and respiratory rhythms of mammals. In a preliminary paper, Gesell and Nyboer (1929a) have reported comparable accelerations in both rhythms during low alveolar oxygen with the vagi intact or cut, the stellates intact or severed, or both stellates and vagi excised, the adrenals being intact in all preparations. These observations confirmed the findings under some of the above conditions by Paul Bert (1878), Gregg, Lutz and Schneider (1920), Jarisch and Wastl (1926), Mathison (1910), and Somervell (1925). Slowing of the heart during

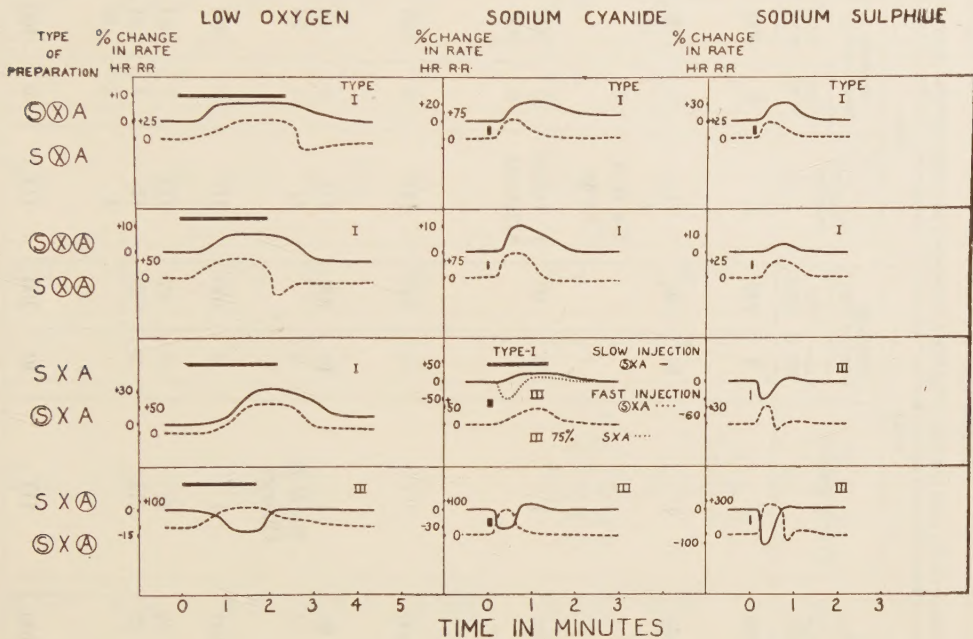


Fig 3. Graphs of predominant changes in cardiac (—) and respiratory (---) rhythms effected by low alveolar oxygen, and the intravenous injections of sodium cyanide and sodium sulphide. The experimental conditions are indicated in the left margin; the duration of gaseous administration by a horizontal line above each pair of curves, and duration of injection by a short vertical line between the curves. Percentage change ($\pm$) in each rhythm is plotted on the ordinates against time in minutes on the abscissae.

anoxemia, however, was observed by Takeuchi (1925), and Gremels and Starling (1926); the former in cats with cardiac innervation intact, artificial ventilation and urethane-ether narcosis, the latter in denervated dog heart-lung preparations.

In the present experiments with the adrenals intact low alveolar oxygen usually accelerated both the heart and respiratory rhythms as in curve type I with all types of innervation, S.X.A., (S).X.A., S.(X).A., (S)(X).A. (See fig. 3.) In one out of 24 S.X.A. dogs there was a late but distinct

NaHCO ₃	{ A....	III II I	16 2 1	88 8 4	III II III	78 22	7 2	5 3	63 37	III I II	5 4 3	42 33 25
	{ (A)...	III I	5 2	72 28	III	100	4	2 1 1	50 25 25	III	7	100
	{ A....	IV I	18 3	86 14	IV I	72 28	5 2	6 1	84 16	IV I	7 1	86 14
	{ (A)...	IV I	7 1	86 14	IV	100	4	5 2 1	72 25 13	II IV III	3 2 1	50 33 17
Na ₂ CO ₃	{ A....	III I	4 3	44 33	III	100	5	6	100	II IV III I	10 5 2 2	53 27 10 10
	{ A....	> R.R. 0 H.R.	2	23								
	{ (A)...	III 0 > R.R. < R.R.	3 3 1	43 43 14	III 0 H.R.	50 25	2 1 25	4 2	67 33	II III	3 2	60 40
	{ A....	I III	8 4	57 29	III I > R.R. 0 H.R.	62 25 13	5 2 1	5	100	II IV > R.R. 0 H.R.	10 5 1	63 31 6
End of in- spiration	{ (A)...	> R.R. 0 H.R.	7	100	III > R.R. 0 H.R.	75 25	3 1	3 2 1	50 33 17	II	5	100

The following additional notations have been used: >, acceleration; <, slowing; and 0, no change in rhythm, R.R., respiratory rate; H.R., heart rate.

* Following an initial acceleration in heart-rate, a slowing below the basal cardiac rate resulted before the end of the low oxygen administration.

TABLE 2

EXPERIMENTAL PROCEDURE	ADRENALS INTACT										ADRENALS CLAMPED									
	(S) (X) A		S (X) A		(S) X. A.		S. X. A.		(S) (X) (A)		S (X) (A)		(S) X (A)		S. X (A)		(S) X (A)		S. X (A)	
	H. R.	R. R.	H. R.	R. R.	H. R.	R. R.	H. R.	R. R.	H. R.	R. R.	H. R.	R. R.	H. R.	R. R.	H. R.	R. R.	H. R.	R. R.	H. R.	R. R.
	H. R.	R. R.	H. R.	R. R.	H. R.	R. R.	H. R.	R. R.	H. R.	R. R.	H. R.	R. R.	H. R.	R. R.	H. R.	R. R.	H. R.	R. R.	H. R.	R. R.
Part I—Average basal rate per minute before experiment																				
	149	13	211	10	138	20	117	18	137	12	225	12	133	17	212	19				
Part II—Average per cent change of rate																				
Low O ₂	+8.7	+26	+7	+75	+19	+42	+30	+62	+7.0	+65	+7	+42	-18 +6	+100	-17 +7	+145				
NaCN.....	+18.6	+46	+8	+90	-42 +22	+37	+56	+145	+10.0	+59	+5	+55	-33	+98	-30	+148				
Na ₂ S.....	+16.0	+59	+7	+75	-51	+66	-42	+145	+3.0	+84	+8	+62	-29	+32	-46	+118				
CO ₂	-10.0	+27	-10	+20	-17	-15	-24	+17 -43	-12.0	+40	-10	+23	-14	+40	-17	+32				
NaHCO ₃	-7.7	+14	-4	+30	-12	+17	-20	+35	-6.3	+12	-3	+14	-8	+20	-11	+15 -18				
Na ₂ CO ₃	+19.0	-40	+13	-31	+22	-38	+48	-44	+20.0	-44	+6	-24	+10	-51	+51 -18	-42				
Mechanical asphyxia end of expiration	+9.0 -6.0	+45	-3	+56	-26	-34	-20 +19	-26	-3.0 0	+25	-3 0	+50	-9	+35 -50	-28	±5				
End of inspiration....	+13.0 -3.0	+40	-3 +5	+50	-30	-45	-26 +18	-50	0	+35	-5 0	+30	-8	+50 -30	-18	-46				

slowing of heart rhythm following an initial acceleration during lowered alveolar oxygen. (See footnote* table 1.)

With adrenals clamped in (S)(X)(A) and S(X)(A) preparations primary accelerations of heart and respiratory rhythms were obtained as in all dogs with adrenals intact. (See fig. 3.) The results are similar to the effects of bulbar anemia in which temporary occlusion of the head arteries produced cardiac acceleration in vagotomized, and in combined vagotomized and stellate-excised preparations in normal or adrenalectomized cats (Coombs, 1924, 1925, 1926).

The reaction to low alveolar oxygen of dogs with adrenals clamped, but with the vagus nerves intact S.X.(A), was frequently different from the observations described above. In these instances the usual acceleration of heart rate was frequently replaced by a slowing of rate during the administration period. An initial increase in respiratory rate generally occurred.⁶ Specifically, 80 per cent of ten (S)X(A) preparations and 61 per cent of eighteen S.X.(A) preparations reacted according to type III (see fig. 3, tables 1 and 2). The remaining reactions were of type I. In most exceptions additional anesthesia was injected before the experiment was begun in order to eliminate irregularities due to extraneous stimuli.

Thus, comparison of experiments in adrenalectomized-preparations, either S.X.(A) or S(X)(A), with those in adrenal-preparations, either S.X.A. or S.(X).A, indicates that the adrenal glands play an important accessory rôle in control of cardiac rhythm during anoxemia. The integrity of the vagus innervation was necessary to the cardiac inhibition frequently obtained in adrenalectomized-preparations.

With these observations in mind the results of sodium cyanide and sodium sulphide on cardiac and respiratory rhythms may be considered.

B. *The effects of intravenous injections of sodium cyanide on heart and respiratory rhythms* (see fig. 3, tables 1 and 2). Little attempt has been made to correlate the changes in cardiac and respiratory rhythms incurred by injection of sodium cyanide in animal or man. Geppert (1889) demonstrated that hydrocyanic acid action is essentially one of asphyxiation, since it acts by decreasing the oxygen absorbed by the tissues and also the carbon dioxide produced by them. Bodine (1924) claims that HCN in acid, neutral, or slightly alkaline media produces intra-cellular acidity in plants and in artificial cells made of living frog skin because of the rapid penetration of HCN molecules. The correlation of continuous changes in numerous factors of respiratory control following intravenous injection of

⁶ One adrenalectomized dog invariably gave a decrease in respiratory rhythm regardless of the experimental procedure, i.e., low O₂, Na₂S, NaCN, CO₂, NaHCO₃, Na₂CO₃ in S.X., (S.)X., S.(X)., (S) (X) preparations produced a slowing of respiratory rate. (Data are not included in table 1.) Severe operative procedures and low resistance of the animal might be the cause of this exception.

sodium cyanide by Gesell, Krueger, Gorham, and Bernthal (1930) is of considerable importance in an interpretation of cyanide action. These workers find that lowered alveolar oxygen and NaCN produce similar metabolic changes in the dog. In a preliminary report, Gesell and Nyboer (1929a) indicated that cyanide augments both cardiac and respiratory rhythms in dogs with adrenals intact in very much the same manner as low alveolar oxygen.⁷

A tabular summary of our experiments on the effects of intravenous cyanide injections in normal adrenal and adrenalectomized dogs is also shown in tables 1 and 2. When the adrenals were intact, sodium cyanide usually produced acceleration of heart and respiratory rates in (S)(X)A, S(X)A, (S)X.A., and S.X.A. preparations with few exceptions. With complete cardiac innervation, S.X.A., 75 per cent of the dogs gave type I response; the remaining 25 per cent were of type II, III, or IV. In (S) X.A. preparations type III response was obtained with rapidly injected cyanide; but slow injections in the same preparations brought about type I response as in the intact animal. (See fig. 3, tables 1 and 2.)

When the adrenals were clamped, the vagus nerves cut, and the stellate ganglia either intact or removed, S.(X)(A) or (S)(X)(A), the responses to sodium cyanide were invariably of type I, i.e., an increase in the cardiac and respiratory rates.

If, however, the vagus nerves were intact, S.X.(A) or (S)X(A), the adrenalectomized dog responded differently to sodium cyanide. These responses resembled those of low oxygen under similar conditions, i.e., a decreased heart rate and an increased respiratory rate resulted as in type III. (See fig. 3 and table 1.) Only one exception, a type I response, was recorded from observations in nineteen dogs. This one dog, however, on rapid injection of sodium sulphide gave a response typical of cyanide, which as will be seen below resembles the typical sulphide response under these conditions.

C. *The effects of sodium sulphide injections.* (See fig. 3, tables 1 and 2.) A detailed report (Gesell and Nyboer, 1929b) of the effects of sodium sulphide in dogs with intact adrenals, showed that intravenous injections in denervated preparations generally produced an increase in cardiac and respiratory rhythms. In experiments with intact innervation, differences in response were evident. In the present report these data are included and correlated with further experiments.

Sodium sulphide effects may be grouped into type I or type III depending on the integrity of the vagus innervation. Type I reaction almost

⁷ Loevenhart, Schlomovitz and Seybold (1922) observed that twenty-five cyanide injections usually less than 0.75 cc. of 0.02 NaCN per kilo in normal, *unanaesthetized* dogs (vagus nerves and stellate ganglia intact) resulted in early cardiac slowing twenty times, cardiac acceleration two times, and no cardiac effect three times.

invariably occurred in vagotomized dogs, whether the stellate ganglia were intact or excised, i.e., (S)(X) or S(X). Type III always occurred in dogs with vagus innervation, whether the stellate ganglia were intact or excised, i.e., (S)X, or S.X. preparations. These results were usually the same before and after adrenalectomy. (See fig. 3, tables 1 and 2.)

Comparing rapid injections of cyanide and sulphide in S.X.A. preparations, it is seen that, whereas cyanide usually accelerated the heart, sulphide usually slowed it. Respiratory rhythm was accelerated by both substances. Under all other conditions, both rhythmic responses showed great similarities with sulphide and cyanide injections. (See fig. 3.)

In view of the similarity of the effects of sodium sulphide, sodium cyanide, and low alveolar oxygen, especially in adrenalectomized dogs, it is sug-

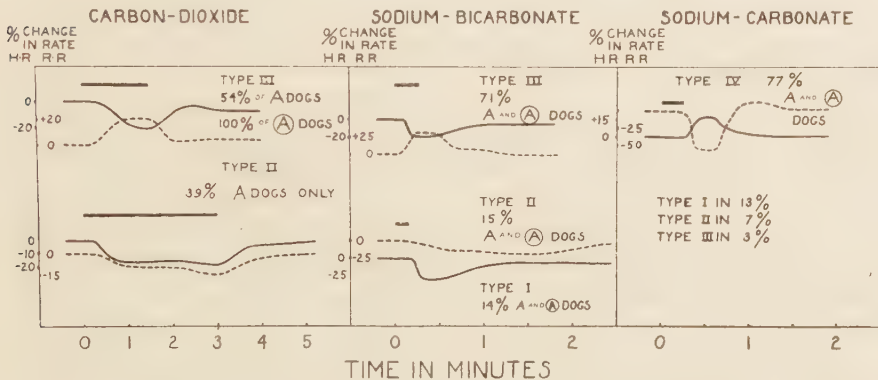


Fig. 4. Graphs of predominant changes in cardiac and respiratory rhythms effected by high alveolar carbon dioxide, and intravenous injections of sodium bicarbonate and sodium carbonate. The preparations with adrenals intact are represented by A, and adrenalectomized preparations by (A).

gested that the chemical changes responsible for the changes in cardiac and respiratory rhythm control may be the same. The irritability of the bulbar vagus centers to these substances, and the inhibitory influence of these substances on the heart rate was most clearly demonstrated in adrenalectomized animals.

D. *The effects of rebreathing carbon dioxide in gas mixtures containing 22 per cent or more of oxygen.* (See fig. 4, tables 1 and 2.) Although considerable work has been done with carbon dioxide as a respiratory stimulant, it was found profitable to repeat many observations on the anesthetized dogs under various conditions of nervous and adrenal gland control. In man, Schneider and Truesdell (1922) found that respiratory rate gradually increased with high alveolar CO_2 . Haldane (1922) states that high alveolar carbon dioxide chiefly increases the depth of breathing and

causes only a moderate increase in frequency. From several hundred experiments on the dog, Gesell (1929a) observed that the common result of high alveolar carbon dioxide and low alveolar oxygen was to produce an increase in rate and depth of breathing. On the whole lowered alveolar oxygen accelerated the rate of respiratory movements more than did increased alveolar carbon dioxide pressure. These experiments indicated that the difference in respiratory rhythmic response to low oxygen and excess carbon dioxide is one of degree.

Waller and Sowton (1896) demonstrated the slowing effects of carbon dioxide on the excised heart of turtle and frog; Jerusalem and Starling (1910) in heart-lung preparations of the dog. Yandell Henderson (1908), working with dogs in which cardiac innervation was intact, found that an inverse relation existed between heart rate and carbon dioxide content of the arterial blood. According to Schneider and Truesdell (1922) the heart rate in man was usually accelerated or unaffected by high alveolar carbon dioxide.

In the present series of experiments with adrenals intact, high alveolar carbon dioxide caused an acceleration or a slowing of respiratory rhythm, whereas the heart was almost invariably slowed (see table 2, part II). A study of the carbon dioxide data in table 1 shows that carbon dioxide elicited all four types of rhythmic reactions; type III occurred in 73 per cent of (S)(X)A preparations, in 33 per cent of S.(X)A. preparations, in 54 per cent of (S)X.A. preparations, and in 59 per cent of S.X.A. preparations. Type II occurred in 27 per cent of (S)(X)A preparations, in 67 per cent of S(X)A preparations, in 31 per cent of (S)X.A. preparations, and in 29 per cent of S. X. A. preparations. Type I reaction occurred only in 15 per cent of the (S)X.A. preparations, and in 8 per cent of the S.X.A. preparations. Type IV occurred only once in the whole series of carbon dioxide observations (in an S.X.A. preparation).

In adrenalectomized dogs, type III reaction invariably occurred if gross tissue abuse was avoided during the operations (see table 1 and fig. 4 and footnote on p. 213). Further experiments, however, must supplement these data to determine the quantitative relations probably existing between the normal and adrenalectomized preparations.

Respiratory acceleration occurred in 61 per cent of all carbon dioxide experiments and slowing occurred in 39 per cent. Cardiac slowing occurred in 93 per cent and acceleration in 7 per cent of all carbon dioxide experiments. The significance of the occurrence of two major types of acute rhythmic reaction (i.e., types III and II), in animals with adrenals intact, and only type III reaction in adrenalectomized dogs, is not understood. (See table 1 and fig. 4.)

E. *The effects of sodium bicarbonate.* (See fig. 4, tables 1 and 2.) The effects of intravenous injections of sodium bicarbonate on pulmonary ventilation, reflex and muscular activity, salivary secretion, and on acidity and

volume flow of lymph and blood have been studied by Gesell and McGinty (1927); Glazer (1929), Winkler (1930), Gay (1931); Eddy (1930); Bronk and Gesell (1927), Gesell (1929b). It has been pointed out that the effects of sodium bicarbonate are diametrically opposite in action to sodium carbonate. That such differences are possibly attributable to opposite effects on the blood carbon dioxide pressure, is supported by experimental data (Gesell, 1923; Gesell and Hertzman, 1926; Gesell and McGinty, 1927).

In the present series of experiments with intravenous injections of NaHCO_3 , acceleration of respiratory rhythm generally resulted, whereas heart rate was generally slowed. (See fig. 4, tables 1 and 2.)

With adrenals intact, type III and type II reactions occurred most frequently with sodium bicarbonate injections and type I least (see table 1 and fig. 4).

In adrenalectomized animals, type III was predominant in (S)(X)(A), S(X)(A), and S.X(A) preparations with bicarbonate injection. Conclusions can not be drawn from the results on (S)X(A) preparations as there are only four experiments and the results of these are variable. (See tables 1 and 2.)

In general, the changes obtained in both rhythms with sodium bicarbonate suggest a great similarity to those obtained with high alveolar carbon dioxide. Summarizing the seventy bicarbonate experiments, type III occurred in 71 per cent, type II, in 15 per cent, and type I in 14 per cent. Respiratory rhythm was accelerated in 85 per cent of these experiments, whereas cardiac rhythm was slowed in 86 per cent.

F. The effects of sodium carbonate. (See fig. 4, tables 1 and 2.) That intravenous injection of sodium carbonate generally causes a decrease in pulmonary ventilation, a lowering of the blood pressure, and a decrease in acidity of the blood and tissues, is accepted. The diametrically opposite physiological effects on respiration of sodium carbonate to those of sodium bicarbonate, are possibly due to the opposite effects on the blood carbon dioxide pressure caused by these experimental agents (Gesell, 1923; Gesell and Hertzman, 1926a; Gesell and McGinty, 1927).

In the present experiments, heart rhythm usually increased while respiratory rhythm usually decreased under the eight conditions of cardiac innervation and adrenal condition. Adrenalectomy had little effect upon the results, as reaction type IV occurred in 82 per cent of all adrenal dogs and in 70 per cent of all adrenalectomized dogs. (See tables 1 and 2 and fig. 4.)

Summarizing the sixty-nine Na_2CO_3 observations under the different conditions outlined, and in different dogs, we find that reaction type IV occurred in approximately 77 per cent of the experiments; type I in 13 per cent; type II in 7 per cent, type III in 3 per cent.

G. The effects of mechanical asphyxia produced at the end of expiration and

at the end of inspiration. (See fig. 5, tables 1 and 2.) The effects of mechanical asphyxia on the hydrogen ion concentration of the cerebro-

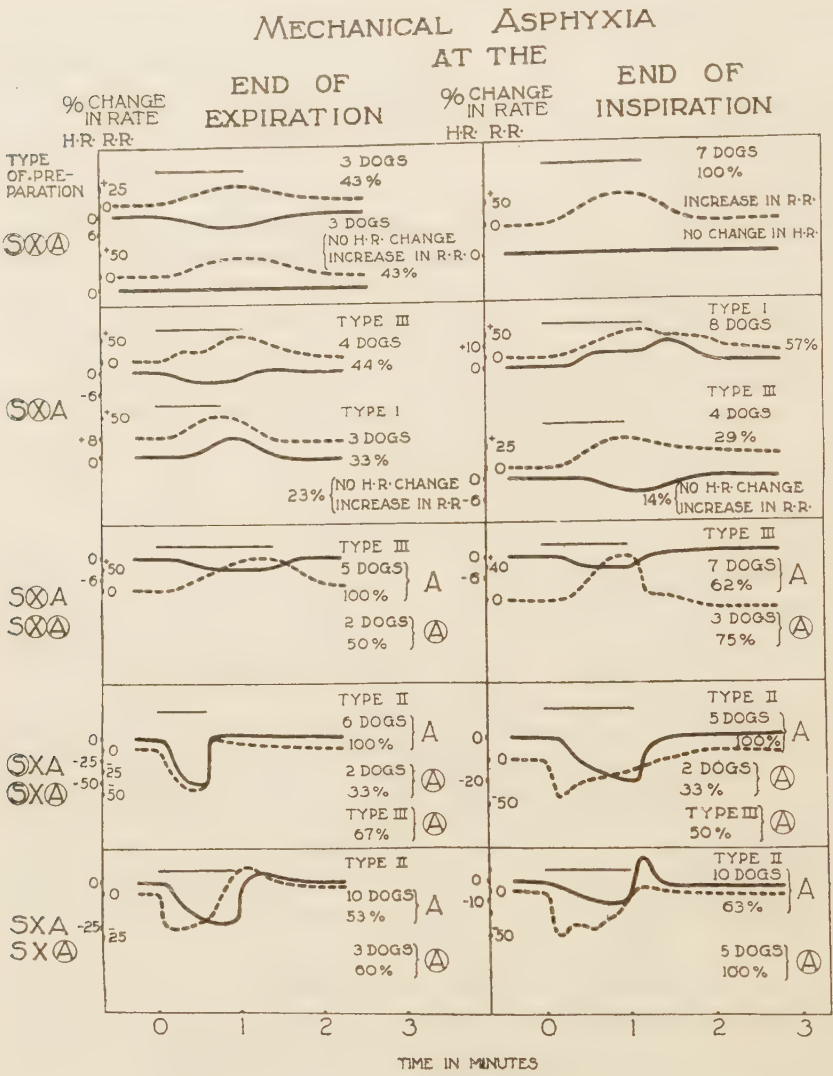


Fig. 5. Graphs of cardiac and respiratory rhythm changes effected by mechanical asphyxia at the end of expiration and at the end of inspiration in the various types of preparations indicated on the left margin of the figure.

spinal fluid, arterial and venous blood, on the reflex response of the tibialis anterior muscle, and on segmental respiratory movements of the dog, have been studied (Gesell and Hertzman, 1927, 1928; Glazer, 1929; Gesell and

Moyer, 1933). The present report considers only the effects on cardiac and respiratory movement rates following asphyxiation for periods of 30 seconds or longer following a normal inspiratory or expiratory movement.

In denervated preparations, (S)(X)A, mechanical asphyxia at the end of expiration produced reactions of type III, 44 per cent; type I, 33 per cent; and in 23 per cent an increase in respiratory movement rate but no change in heart rate when the adrenals were intact. In adrenalectomized and denervated preparations, (S)(X)(A) type III occurred 43 per cent, but in the remaining 67 per cent no heart rate change was demonstrable while respiratory movements were either accelerated or retarded during the asphyxial period. With asphyxiation at the end of the inspiration, however, type I occurred most commonly (57 per cent of fourteen dogs with adrenals intact (S)(X)A; type III occurred 29 per cent, and in 14 per cent the heart rate did not alter while respiratory movements accelerated. In adrenalectomized preparations, (S)(X)(A), heart rate was never observed to retard or accelerate while respiratory efforts were invariably accelerated during asphyxia at the end of inspiration.

In vagotomized S(X)A or S(X)(A) preparations reaction type III was predominant. Occasionally heart rate did not change during the asphyxial period. Retardation of respiratory rate sometimes occurred, but acceleration of heart rate, rarely.

When the stellate ganglia were excised either type of asphyxia invariably effected reaction of type II when the adrenals were intact, (S)X.A. In adrenalectomized (S)X(A) preparations type III was predominant but type II was not uncommon. (See table 1.) The irritability of the vagi may have been partially altered here due to previous experimenting with cold block. This may explain the occasional accelerating respiratory rhythm in this procedure.

In normally innervated dogs, S.X(A) and S.X.A., reaction type II was predominant during either type of asphyxia if the adrenals were functional or clamped. (See table 1.) Types 1, 3 and 4 were also observed. In S.X.A. experiments acceleration of the heart was obtained when the basal heart rate was low (approximately 80) and slowing of the heart when the basal rate was higher (approximately 127).

Summarizing, it appears that the integrity of the vagus was necessary to produce a primary reflex respiratory slowing as observed in S.X.A., S.X.(A), (S)X.A. and (S)X(A) experiments. Respiratory acceleration usually occurred when the vagi were cut or excised (S(X)A, S(X)(A), (S)(X)A and (S)(X)(A)). Slight slowing of the heart takes place in spite of predominant sympathetic innervation in S(X)A and S(X)(A) experiments. Marked cardiac slowing usually occurred in S.X.A., (S)X.A. S.X.(A), and (S)X(A) experiments. Cardiac acceleration sometimes observed in (S)(X)A experiments with either type of asphyxia was not elicited

in adrenalectomized preparations (S)(X)(A). Here, mechanical asphyxia at the end of inspiration never altered heart rate; whereas mechanical asphyxia at the end of expiration sometimes slowed it. Thus it appears that the acceleration in (S)(X)A experiments was of adrenal gland origin. Slowing was probably due to a greater accumulation of metabolic products at the cardiac pace-setter during mechanical asphyxia at the end of expiration as compared with asphyxia experiments at the end of inspiration. There appears to be a close analogy with similar effects under those conditions produced by carbon dioxide administration.

CORRELATION AND DISCUSSION. The corresponding experimental results are briefly correlated according to type of reaction and type of preparation in table 3. Only the reactions which occurred most frequently in the various preparations are considered in this table. In reactions I and II the change of rate in cardiac and respiratory movements are parallel (I shows acceleration and II slowing of both rhythms). In reaction III and IV there is an opposite response of cardiac and respiratory rhythm (IV shows early acceleration of heart and early slowing of respiratory movements, whereas III shows early slowing of the heart and early acceleration of respiratory movements).

The results in the denervated preparations, (S)(X)A and (S)(X)(A), are probably the best criteria for observations of the most elementary effects produced by the experimental agents studied. Therefore, in view of the similarity of reaction of both rhythms to low O_2 , Na_2S , and $NaCN$, it is suggested that there may be common fundamental factors responsible for acceleration of the heart and respiration in these preparations. On the other hand, in view of the dissimilarity between heart and respiratory rhythms when CO_2 and $NaHCO_3$ and Na_2CO_3 are the experimental agents, it appears that the fundamental factors controlling the rhythms are different or that additional factors are involved. The apparent antagonistic effects on the heart rate of these two sets of procedures, (i.e., acceleration by low O_2 , Na_2S , $NaCN$, and Na_2CO_3 , and slowing by CO_2 , $NaHCO_3$), cannot be ascribed to an extrinsic nervous activity, since the heart is denervated. Neither can it be ascribed to the liberation of adrenal gland secretions, since similar results are usually obtained in completely adrenalectomized dogs, nor can it be ascribed to known accessory hormones, which are not activated in fully anesthetized dogs under urethane narcosis (Cannon, 1931). Therefore, the only known agent left which may determine the change in rhythmic activity is a direct chemical or physico-chemical control of the cardiac pace-setter. As regarding respiratory movements, we may have a direct, a reflex chemical, and a reflex mechanical control of the pace-setter. At present, however, there is no immediate evidence as to the exact nature of the controlling mechanism. Its determination is beyond the scope of these experiments. Gesell (1926) has tentatively

TABLE 3
Tabular correlation of predominantly similar experimental results according to reaction type and type of preparation

TYPE OF REACTION	ADRENALS INTACT				ADRENALS CLAMPED			
	(S)(X)A	S(X)A	(S)X.A.	S.X.A.	(S)(X)(A)	S(X)(A)	(S)X(A)	S.X(A)
I	Low O ₂ NaCN Na ₂ S +*(E.E.) *(E. I.)	Low O ₂ NaCN Na ₂ S	Low O ₂ NaCN(slow)	Low O ₂ NaCN	Low O ₂ NaCN Na ₂ S	Low O ₂ NaCN Na ₂ S		
II	CO ₂		(E.E.) (E.I.)	E.E.) *(E.I.)			*(E.E.) *(E.I.)	(E.E.) (E.I.)
III	CO ₂ NaHCO ₃ *(E.E.) *(E.I.)	NaHCO ₃ (E.E.) (E.I.)	NaCN(fast) Na ₂ S CO ₂ NaHCO ₃	Na ₂ S CO ₂ NaHCO ₃	CO ₂ NaHCO ₃ (E.E.) (E.I.) †(E.I.)	Low O ₂ NaCN Na ₂ S CO ₂ *(NaHCO ₃) *(E.E.) *(E.I.)		Low O ₂ NaCN Na ₂ S CO ₂ NaHCO ₃
IV	Na ₂ CO ₃	Na ₂ CO ₃	Na ₂ CO ₃	Na ₂ CO ₃	Na ₂ CO ₃	Na ₂ CO ₃	Na ₂ CO ₃	*(Na ₂ CO ₃)

+E.E. indicates mechanical asphyxia at end of expiration; E.I. indicates mechanical asphyxia at end of inspiration.

† Heart rate remained unchanged during asphyxial periods.

* Uncertain. See table 1.

proposed an electrochemical hypothesis of physiological rhythm control, which includes oxidation-reduction potentials as a factor. The similar or dissimilar response of the cardiac pace-setter and the respiratory pace-setter to apparently similar chemical stimuli, have been pointed out with special reference to the denervated heart preparations. The parallelism in cardiac and respiratory rhythms in denervated preparations, following low oxygen, sodium cyanide and sodium sulphide administrations, support the postulate of a common mechanism of rhythm control. The lack of parallelism of both rhythms in (S)(X)(A) preparations following mechanical asphyxia at the end of expiration, carbon dioxide, sodium bicarbonate and sodium carbonate administrations, do not directly support this postulate.

During low alveolar oxygen and on injection of sodium cyanide, the auxiliary activity of the adrenal glands on cardiac and respiratory rhythms was evident in preparations with vagi and adrenals intact, (S)X.A. or S.X.A., particularly if these results were compared with those obtained in adrenalectomized-preparations with vagus innervation intact, (S)X(A) or S.X(A). The accelerated heart, (as in type I reaction), typical of the adrenal-preparation, was seldom observed in the adrenalectomized-preparation during these procedures; hence impaired oxidations resulted in inhibition of the heart through the vagus, due to the absence of the accelerating component of the adrenal gland. This inhibition was especially true in (S)X(A) preparations since both nervous and adrenal accelerating components were lacking. Vagotomy abolished this cardiac slowing phenomenon.

SUMMARY

This study attempts to compare changes in cardiac and respiratory rhythms effected by common changes in physiological conditions in the dog. The effects of low alveolar O_2 , high alveolar CO_2 , mechanical asphyxia, and of injections of $NaCN$, Na_2S , $NaHCO_3$, and Na_2CO_3 were recorded in eight types of preparations, in which the function of the vagus nerves, stellate ganglia and adrenal glands was controlled. Morphine-urethane anaesthetized dogs were used.

Carbon dioxide or sodium bicarbonate administrations usually slowed cardiac rhythm in most preparations. These substances either accelerated, slowed, or had no effect on respiratory rhythm. On the other hand sodium carbonate injections usually slowed respiratory rhythm and accelerated cardiac rhythm.

Mechanical asphyxia almost invariably accelerated respiratory rhythm in vagotomized, and in combined vagotomized and stellate-excised preparations with adrenal glands intact or occluded from the circulation. With adrenals intact, the cardiac rhythm was either accelerated, slowed or un-

altered during asphyxia of either type. If, however, the adrenals were occluded, moderately short asphyxias at the end of inspiration never altered the heart rhythm; whereas asphyxia at the end of expiration frequently caused a slight slowing. When the vagi nerves were intact marked slowing of both cardiac and respiratory rhythms resulted most frequently during asphyxia of either type.

Both rhythms were accelerated in vagotomized, or combined vagotomized and stellate-excised preparations, by low alveolar O_2 , NaCN, and Na_2S , whether the adrenals were intact or clamped. When the vagus nerves were intact, rhythmic responses to low alveolar O_2 and to NaCN differed in adrenal and adrenalectomized dogs; i.e., adrenal preparations showed acceleration of both rhythms, whereas adrenalectomized preparations usually showed a retardation of cardiac rhythm and simultaneous acceleration of respiratory rhythm. Vagotomy abolished these differences.

It is concluded that in denervated preparations (combined vagotomy and stellate-excision), the effects of the low alveolar O_2 , NaCN, and Na_2S were very similar on both cardiac and respiratory rhythms. Less agreement in both rhythms was obtained with CO_2 and $NaHCO_3$ administrations and during mechanical asphyxia. Sodium carbonate injections usually produced opposite results in cardiac and respiratory rhythms. Until further evidence is forthcoming, conclusions regarding the similarity of a common mechanism of physiological rhythm control must be postponed.

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